Organ model seeks greatest good

"There are still people who die waiting for lung transplantation," says DMS pulmonologist Jeffrey Munson, M.D. The reason is that there are simply not enough donated organs to meet the demand. Munson has studied this problem from many angles, including, recently, comparing the benefits of transplanting two lungs versus a single lung.

For patients with chronic obstructive pulmonary disorder (COPD), a bilateral lung transplantation (BLT) can increase survival compared to a single lung transplantation (SLT). But bilateral transplants reduce the number of lungs available to other patients.

To examine the tradeoffs, Munson and a team of researchers created a computer model of two identical groups of 1,000 simulated patients, whose characteristics and diagnoses were based on real patient data. All the patients needed transplants, as a result of either COPD or other lung diseases for which SLT is usually as effective as BLT. In one group, patients were on a waiting list for BLT. Those in the other group received SLT. The team then tracked simulated patient outcomes over a two-year period, examining movement up and down a waiting list, the number who received transplants, the number who died, and post-transplant survival. The results were reported in the *American Journal of Respiratory and Critical Care Medicine*.

Results: Overall, the SLT arm of the study did better. More patients received transplants (809 versus 758) and fewer died while waiting (157 versus 199). The total years survived post-transplant was about the same for both groups (4,586 years for SLT; 4,577 years for BLT). Munson believes the results show that SLT may be a better approach in terms of the benefit to society as a whole.

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But when the researchers simulated scenarios with shorter waiting lists and more lungs available for donation, patients lived longer after a BLT. And the outcomes varied by region as well. One northeastern region had 368 fewer years of total survival and 75 more deaths on the waiting list for BLT. But a region in the western U.S. had 215 more years of survival and just 14 more deaths for BLT.

So, Munson says, the issue comes down to a tricky ethical question as to what is the most important outcome. "Is it the number of people you transplant or is it the total survival of the transplant population?" he says. "You can make an argument for both."

Munson's hope is that the study encourages more dialogue on this tough issue. "When you decide to do mostly BLT in your COPD population, that has implications for other patients on the transplant list, and we need to talk about what those implications are," he says. Traditionally, he adds, doctors have tried to take care of the individual in front of them, without considering the implications for other patients. But given limited resources, he says, "maybe that blind allegiance to the individual should be reconsidered." MATTHEW C. WIENCKE

JON GILBERT FOX

Eastman, a professor of pharmacology and toxicology, has been at DMS since 1989.

Is cancer combo *too* effective?

A test that pitted two drugs against leukemia cells produced some promising results—perhaps too promising, cautions lead researcher Alan Eastman, Ph.D. He has long been interested in the dynamics that lead to the death of cells, particularly cancer cells. Several years ago, he and other researchers in his lab were examining the drug vinblastine when they discovered something new. Eastman says it was well established that vinblastine interferes with the process of cell division and can eventually kill leukemia cells, a process that can take up to about 24 hours. "Everybody has accepted that as a mechanism of action for this family of drugs," he says. "They're highly potent and they're used in cancer chemotherapy."

But when Eastman suppressed a family of proteins—called Bcl-2 proteins—that can prevent the death of cells, vinblastine was able to kill cells within just a few hours. That finding led Eastman to wonder whether combining a drug that inhibits Bcl-2 proteins with vinblastine would be an effective treatment against leukemia. So he tested a combination of dinaciclib (a drug that suppresses specific Bcl-2 proteins) and vinblastine on leukemia cell lines from about 40 patients. As he reported in *Cancer Biology and Therapy*, the combination killed every leukemia cell in most cell lines within about four hours.

But the success comes with a caveat, says Eastman. "The downside is it's almost too effective." The problem, he explains, is that a drug that's so widely effective may be more apt to kill normal cells as well, whereas a drug that kills only a few cell lines may be targeting a specific vulnerability perhaps not present in normal cells.

Safe: Yet so far, the combination appears to be safe. When normal white blood cells were exposed to the drugs, there was no greater cell death than expected, and Eastman says previous clinical trials using dinaciclib have shown that patients can tolerate the drug. With these results in hand, he hopes to move forward with clinical trials. "I think it has some real potential for therapy," he says, even though, he emphasizes, there is still much left to be learned. AMOS ESTY